EXECUTIVE SUMMARY

HEAD and NECK CANCER WORKSHOP
February 21-23, 1999
Bethesda Marriott
Bethesda, MD

A priority setting workshop on head and neck cancer was convened on February 21-23, 1999 in Bethesda, MD to address the current status of research in this area and to formulate recommendations for future research in head and neck cancer. The workshop was a combined effort of The National Institute of Dental and Craniofacial Research, The National Cancer Institute and The National Institute on Deafness and Other Communication Disorders. Two outstanding investigators, Dr. Waun Ki Hong and Dr. David Sidransky, served as chairmen for this workshop. Dr. Waun Ki Hong is Professor and Chairman of the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center. Dr. David Sidransky is Professor of Otolaryngology/Head and Neck Surgery, Professor of Cellular and Molecular Medicine and Professor of Oncology at Johns Hopkins University School of Medicine.

The scope of potential opportunities in head and neck and cancer was established in presentations by each of the chairmen in the opening session. Following were four plenary sessions: Etiology of Head and Neck Cancer, Biology of Head and Neck Cancer, Translational Research Infrastructure, and Translational and Clinical Research. Each of these four plenary sessions were comprised of two overview presentations after which the participants joined break out groups to discuss a number of preselected topics and make research recommendations appropriate for each of the assigned subjects which were than reported to the entire group of participants.

It is now well recognized that cancers are genetic diseases in which a progression of genetic aberrations is involved in the process of carcinogenesis and subsequent invasion and metastasis. Research concerning the genetic bases for the regulation of cell differentiation, proliferation, motility and apoptosis is rapidly increasing, as are technological advances that facilitate assessment of these processes. Despite this progress, however, the survival of patients with head and neck cancers has not markedly improved over the past thirty years. In addition, major deficiencies remain in the amelioration of the extreme disfigurement and debilitation resulting from these particular tumors and the current therapies used for their treatment. It is, therefore, imperative to escalate research concerning head and neck cancers, identify new avenues for exploration and move relevant findings into the clinical arena.

The intent of this workshop was to encompass all aspects of head and neck cancers through efforts to prevent their occurrence, to detect and treat their probable future occurrence by investigations of premalignant lesions, to detect and treat these tumors at the earliest possible stage, to develop novel mechanisms for treatment and to improve

the quality of life and rehabilitation of patients with these malignancies. The recommendations from this workshop will provide guidance for developing a multidisciplinary collaborative approach to reducing the mortality and morbidity associated with head and neck cancers. This summation of the workshop highlights the presentations and break out groups discussions, details of which are included in the Workshop Report.

KEYNOTE ADDRESSES-Presentations by the Chairmen

Molecular Targeted Therapy and Chemoprevention in Head and Neck Cancer
Waun Ki Hong

A number of advances regarding head and neck cancers have been made in the last decade including the identification of molecular markers and genetic polymorphisms, utilization of combined treatment modalities, preservation of organ function and the effective application of chemopreventive therapies. Intensive research efforts are focussed on the future application of molecular targeted therapy. Promising candidates for new treatment regimens include agents that inhibit epidermal growth factor receptor dependent signaling pathways, farnesyl transferase inhibitors, anti-angiogenic factors, cell cycle inhibitors and interferons. Significant progress has been made in reversing the early steps of the tumorigenic process with retinoid-based chemoprevention. Phenotypic reversion of certain premalignant lesions has been achieved. Current emphasis is also on achieving complete molecular responses, the determination of which is dependent on the ongoing identification of genetic aberrations occurring at different stages of carcinogenesis.

Unraveling the Molecular Changes in Head and Neck Squamous Cell Carcinoma: Hope for the Next Century
David Sidransky

Tobacco and/or alcohol use contributes very significantly to the development of head and neck cancers. The susceptibility of individuals to these carcinogens can be attributed, at least in part, to polymorphisms in the enzymes involved in their metabolism. “High-risk” human papillomaviruses have also been implicated in the etiology of head and neck cancers. The progression of these cancers from benign hyperplasia to invasive cancer results from sequential genetic aberrations, a process that is currently being delineated. Identifying these genetic alterations not only provides strategic points for intervention but can be applied to the diagnosis of sites for unknown primary tumors that have metastasized and precisely defining tumor margins. Clonal genetic changes have also been successfully detected in the saliva and serum of head and neck cancer patients. Thus, molecular analysis will be invaluable for early detection, staging, monitoring and assessing response to therapy. New genes need to be identified and these and known genes evaluated for their diagnostic and prognostic potential. Subsequently, it is critical that this information be applied to the clinical setting which, in turn, is dependent on the development of high through-put methodologies.

PLENARY SESSION I-Etiology of Head and Neck Cancer

Peter Shields addressed the epidemiology of head and neck cancer and the general paradigm for cancer epidemiology which differs from traditional epidemiology in that it is multigenic in nature, exhibits considerable inter-individual variation, and is affected by multiple environmental factors including tobacco and alcohol. Susceptibility genes, cell cycle control genes, DNA repair mechanisms and apoptosis induction are all implicated in the initiation and progression of these diseases.

Margaret Spitz discussed quantitative risk assessment for head and neck cancers. The major goal of research in this area is to identify high risk subgroups and target these for intensive behavioral interventions, surveillance and enrollment in chemopreventive programs. Correlations of polymorphisms in susceptibility genes, DNA adduct profiles and DNA repair capacity with biomarkers are providing useful criteria for selection of appropriate populations.

PLENARY SESSION II-Biology of Head and Neck Cancer

Thomas Carey summarized the complex cytogenetic changes occurring in HNSCC. He emphasized the importance of identifying the consistent chromosomal alterations and delineating the sequence of these changes. Certain genetic markers as well as antibodies to at least one tumor suppressor gene are providing useful information concerning the predictability of responses to different therapeutic regimens.

Jennifer Rubin Grandis described studies of the regulation of TGFα and EGFR, both of which are overexpressed in HNSCC. The extent of upregulation of both molecules occurs at the level of transcription and may have significant prognostic value. The levels of TGFα and EGFR can be manipulated by various genetic mechanisms and correlated with biological responses including activation of certain signal transducers and activators of transcription proteins (STAT proteins), extent of tumor growth and rate of apoptosis.

PLENARY SESSION III-Translational Research Infrastructure

Elizabeth Hammond discussed issues related to tissue acquisition, tissue allocation, tissue banking and immunohistochemical methods. The importance of appropriate and standardized tissue preparation, block selection and tracking was emphasized. The process of tissue allocation to various investigators must also be standardized and guidelines established for this purpose. Uniform immunohistochemical techniques and reagents should be utilized and methods of quantitation standardized.

J. Jack Lee addressed statistical methodology and database management related to the analysis of HNSCC data. The objectives include collection of high-quality data, efficient entry, management and retrieval of data as well as development and proper application of statistical methods. Considerations in data analysis include such

variables as the number of patients, number of biomarkers, assays used for biomarkers and number of biopsies per patient. Some of the complexities of managing databases include centralization of information; management of multicenter heterogeneous databases; adaptability and flexibility of the database; and security and proprietary issues.

PLENARY SESSION IV-Translational and Clinical Research

Everett Vokes provided an overview of the current status of treatment regimens for HNSCC. Concomitant chemoradiotherapy has provided a statistically significant survival benefit in HNSCC. Improvements have also been achieved in the preservation of organ (larynx) function. There is support for treatment intensification and research to reduce resultant toxicities is warranted. As the control of local and regional disease becomes more effective, the clinical management of distant disease becomes more relevant and need to be considered in new trials.

Arlene Forastiere summarized treatment for patients with advanced recurrent disease. Among the difficulties in treating these patients are excessive toxicities and comorbid disease. Thus, novel therapies that are efficacious, tolerable and amenable to chronic administration are needed. These might include receptor antagonists, cell cycle regulators, apoptosis inhibitors, angiogenesis inhibitors, gene therapy and matrix metalloproteinase inhibitors.

FINAL RECOMMENDATIONS FROM PLENARY WRAP-UP SESSION

RECOMMENDATIONS FROM THE CHAIRMEN

1. Hold a Head and Neck Cancer Priority Setting Workshop every 3 years.
2. Establish Head and Neck Cancer **SPOREs** (include translational research).
3. Provide supplemental funding for translational research consortia and working groups to address and implement:
   - Tissue bank and pathology standardization
   - Biomarkers, databases and biostatistics
   - Translational, chemoprevention and therapeutic trials.
4. Integrate molecular approaches with detection and staging strategies.
5. Integrate molecular approaches with therapeutic interventions.
6. Enhance interactions and collaborations among the four **Oral Cancer Research Centers** and cooperative groups.
7. Establish funding to foster young physicians/scientists (including translational researchers) and biostatisticians through Clinician Scientist Awards and other funding mechanisms.

RECOMMENDATIONS FROM THE BREAKOUT GROUPS

RECURRENT THEMES

1. Support young investigators.
2. Recruit new investigators to the HNSCC field.
3. Develop a consortium of dentists/oral surgeons to recruit patients with premalignant lesions.
4. Establish tissue banks.

PLENARY SESSION I-ETIOLOGY of HEAD and NECK CANCER

GROUPS I & II-Epidemiology and Special Populations/Genetics and Environment

1. Initiate large studies of head and neck cancer etiology that incorporate:
    - ***A.*** A network of institutions capable of recruiting large numbers of well-characterized head and neck cancer cases and population-based controls with flexible designs to allow for rolling case-control studies that encompass a central specimen repository and is directed by an oversight committee.
    - ***B.*** Testing and validation of new high throughput technologies and testing of well-formulated hypotheses.
    - ***C.*** Nested case-control research of head and neck cancers in well-designed cohort and chemoprevention studies.
    - ***D.*** Exploration of genotype-phenotype relationships.

2. Explore new etiologies (gene-environment interactions and novel risk factors). Support hypothesis driven, mechanistic investigations (carcinogen metabolism, DNA repair, cell cycle control and apoptosis) in equal balance with technology driven studies of genes identified.

3. Promote research concerning environmental factors including different types of tobacco products, viruses, alcohol, nutrition and chronic irritation as well as the influence of immune system dysfunction.

4. Explore epigenetic mechanisms involved in the etiology of head and neck cancers.

5. Support studies of special populations: race, ethnicity, gender, individuals with early and/or premalignant lesions, nonsmokers, nondrinkers, former smokers, young individuals with head and neck cancers, specific genotypes, patients with second primaries or recurrences, familial aggregations.

6. Provide supplementary funding for emerging and expensive high throughput technologies.

GROUP III-Genetics and Human Papillomaviruses

1. Confirm evidence that HPV-positive tumors have a better prognosis than HPV-negative tumors.

2. Support research to definitively resolve the presence and expression of HPV genes in oropharyngeal and tonsillar cancers.

3. Support studies to elucidate the molecular pathways affected by HPV gene products.

4. Conduct multicenter trials and international studies to recruit adequate numbers of appropriate cohorts.

5. Assuming that a role for HPV is firmly established, develop antipapilloma therapies and preventive methods with vaccines and gene therapy.

6. Explore the ethnic disparity for laryngeal papillomatosis and the genetic susceptibility to HPV-related papillomatosis and carcinogenesis.

GROUP IV-Behavioral and Social Aspects

1. Promote prevention of tobacco and alcohol use in healthy populations, premalignant populations, patient populations under treatment and survivors. Address the needs of lower income and low-literacy groups. Identify tailored tobacco cessation interventions applying effective AHCPR/NCI treatments and step care models.

2. Establish the validity of biomarkers for genetic susceptibility and link early detection or genetic susceptibility markers with behavioral issues.

3. Conduct research related to quality of life and organ function in patients who have undergone organ preservation treatment, emphasizing long-term follow-up.

4. Conduct research on rehabilitation needs to identify optimal candidates for prosthesis use, reconstructive surgery, referral to speech pathologists, etc.

PLENARY SESSION II-BIOLOGY OF HEAD AND NECK CANCER

Group I-Growth and Differentiation

1. Refine and/or develop new methodologies and reagents to study growth, differentiation and apoptosis including:
   Development of *in vitro* models for normal, premalignant and malignant cancer.
   Development of three-dimensional models of dysplasias and epithelial/stromal interactions.
   Validation of the clinical relevance of these models *in vivo*.

2. Establish a national repository of well-characterized cell lines and strains.

3. Develop technologies to facilitate assessment of multiple end points utilizing minimal tissue.

4. Investigate mechanisms of cell cycle regulation in HNSCC.

5. Elucidate the role of the immune system in development, maintenance and treatment of HNSCC.

GROUP II-Genetic Instability

1. Identify relevant pathways for genetic instability in HNSCC by studying genes, interactions of genes and interactions of genes and the environment. Differential expression assays using stable and unstable cells, tissues and microdissected tissues should be employed and cooperating families of instability pathways identified.

2. Determine genetic instability mechanisms using *in vivo* model systems.
   Define genetic instabilities in young patients with low carcinogen exposure and nonsmokers.
   Develop transgenic/knockout and crosses of transgenic/knockout mouse model systems.

3. Develop strategies for reducing or reversing genetic instability mechanisms by targeting treatment of unstable cells (e.g. lymphoblastoid cell lines and other sensitive cell lines) and tissues with relevant genes.

4. Focus initial attention on candidate genes including cyclin D1 and other cyclins, cell cycle genes, p16, CDK4 and 6, aurora-like kinases, apoptosis-related genes such as Bcl-X_L and Bcl-X_S and the HPV related genes E6 and E7. Combinations of genes need to be explored.

GROUP III-Molecular Progression

1. Develop uniform tissue processing protocols for diagnosis and tissue banking with established links to clinical and epidemiologic databases.

2. Establish an informatics structure for high-throughput genome-wide analysis.

3. Develop a genotypic/phenotypic approach for multifactorial analysis of specific sites and special populations (e.g. young adults, elderly, racial/ethnic groups).

4. Validate existing markers.

5. Identify new biomarkers according to different pathway analyses.

6. Develop guidelines for the appropriate use of new and existing biomarkers.

GROUP IV-Angiogenesis and Metastasis

1. Identify improved predictive markers for risk of local invasion, regional metastasis, distant metastasis and the negative functional impact of tumor course or treatment of the tumor.

2. Develop novel therapies for invasive and metastatic HNSCC (e.g. metalloproteinase inhibitor therapy).

3. Identify angiogenic factors produced by HNSCC and identify the most effective inhibitors (e.g. anti-vascular endothelial growth factor agents).

4. Determine the potential predictive value of vascular density on outcome.

5. Develop innovative models using transgenic mice, murine tumors and human tumors in nude mice as well as fresh or frozen human tissues from tumors at various stages of progression.

PLENARY SESSION III-TRANSLATIONAL RESEARCH INFRASTRUCTURE

Group I-Animal Models

1. Develop additional mouse models of HNSCC (the mouse appears to be the model of choice since it is most amenable to genetic manipulation).

2. Utilize appropriate genetically modified mouse model systems to explore etiology, pathogenesis, and progression.

3. Utilize appropriate genetically modified mouse model systems to examine mechanisms of carcinogenesis initiated by agents such as tobacco and alcohol.

4. Adapt transgenic mouse models to target genes to oral epithelial cells (e.g. utilize keratin promoters, Epstein-Barr ED-L2, etc.)

Group II-Molecular Databases and Specimen Registries

1. Convene a task force of interested parties and individuals with expertise in the area to create a prototype database incorporating common database definitions, formats and links to methods used to acquire data. Development of the prototype, which will necessitate highly flexible committed funding (not grants), should link existing epidemiology, genetic marker and tissue bank databases as well as linkage of data with methods utilized.

2. Based on the prototype, create a standardized database, explore the possibility of putting data collection instruments on the Internet (with secured access).

3. Encourage use of the database by all involved investigators possibly by requesting that grant applicants who will be storing materials utilize the database.

4. Enhance access to patients, samples and preneoplasias.

GROUP III-Biomarker Analyses

1. Establish biomarker tissue banks using standardized processing, standardized methods, controls and linkage with other tissue banks and other databases.

2. Provide standardized rewards to surgeons/pathologists for specimen procurement.

3. Recruit/retrain high-quality biostatisticians to develop better statistical methods to address the analysis of extensive biomarker data and address multiplicity issues (e.g. multiple end points, multiple covariates, subset analysis, etc.)

4. Conduct prospective and retrospective biomarker validation studies and utilize information from these studies to derive criteria for standard methodologies. Promote reporting standards for biomarkers described in publications in peer-reviewed journals to permit meta-analysis.

GROUP IV-Molecular Methodologies: Pitfalls and Problems

1. Standardize methodologies, reagents and control reagents for use by individual researchers, investigators conducting small multilaboratory trials as well as investigators conducting large trials and intergroup studies. A series of common and easily available positive and negative controls needs to be made accessible and a mechanism for periodically updating and adding to this collection needs to be implemented.

2. Allow small laboratories access to collections of specimens that are of sufficient size to permit meaningful statistical analyses.

3. Markedly expand mechanisms for teaching methodology. Hands-on courses (similar to those provided by AACR) or the development of Internet-based manuals could be considered.

4. Establish publication guidelines for biomarkers to improve the reproducibility of studies through stringent manuscript review.

PLENARY SESSION IV-TRANSLATIONAL and CLINICAL RESEARCH

GROUP I-Chemoprevention

1. Increase patient accrual including high risk patients who do not have cancer, individuals with premalignant lesions and previously treated patients through a network of dentists, oral surgeons and oncologists.

2. Develop biomarkers to identify patients at increased risk, assess biologic effects of chemotherapeutic agents in target tissue and develop surrogate markers for use as end points.

3. Select chemopreventive agents by conducting high throughput screening of new agents, utilizing animal models to develop more effective chemopreventive agents, refining dose and schedule regimens, establishing appropriate toxicity profiles and assessing combinations of agents in Phase III trials.

4. Address behavioral and social issues including the low accrual of minorities, offering appropriate alcohol and/or tobacco cessation counseling and considering opportunities for international collaboration for recruitment of high risk patients.

GROUP II-Organ Preservation

1. Expand organ preservation trials to non-larynx sites.

2. Include studies of biomarkers and predictors of outcome, quality of life measures, functional assessments, evaluation of treatment cost, and long term morbidity in all organ preservation trials.

3. Initiate new organ preservation trials for the larynx and hypopharynx to extend the knowledge gained from the VA and the RTOG 9111 trials.

4. Initiate pilot studies (small trials) of organ preservation incorporating biologic agents with a focus on decreasing second primary tumors and distant metastases to improve survival.

GROUP III-Molecular Early Detection

1. Develop signature markers for identification of earliest stage disease, aggressiveness and after treatment surveillance for recurrent disease.

2. Develop consortia to collect premalignant specimens.

3. Standardize tools and guidelines for a tumor repository and validate these technologies and processes.

4. Enhance access to high throughput technology for rapid assessment of markers.

5. Refine definitions of at-risk populations including both social factors (marijuana use, tobacco and alcohol use and sexual practices) and genetic factors.

GROUP IV-New Therapeutic Interventions

A. Anti-Angiogenesis

1. Evaluate single anti-angiogenesis agents in Phase I/II trials to establish proof of concept.

2. Conduct Phase I trials of combinations of anti-angiogenesis agents, anti-angiogenesis agents in combination with chemotherapy and anti-angiogenesis agents in combination with radiation therapy.

3. Validate serum markers in correlations between serum markers and tumor surrogate markers, serum markers and histology, and serum markers and response/survival.

4. Establish a tissue and serum bank.

5. Determine microvessel density and tumor vascularity of different tumor types for the selection of sites most amenable to angiogenesis inhibitors.

B. MMPIs/Anti-EGFR

1. Integrate basic science research and clinical research to enhance knowledge of the biology of the normal epithelium and cancerous tissue.

2. Develop *in vitro* and animal models to study the effects of MMPIs on extracellular matrix proteins and to determine which substrates are overexpressed.

3. Develop reference laboratories to standardize and validate methods for EGFR and MMP measurement.

4. Establish a research consortium of two to four centers with HNSCC expertise that would incorporate the development and assessment of new EGFR antagonists and the assessment of the effectiveness of MMPIs with broad specificity.

C. Immunotherapy

1. Study mechanisms of tumor-induced immunosuppression (which is more pronounced in HNSCC patients than other cancer patients).

2. Investigate mechanisms for overcoming tumor-induced immunosuppression through upregulation of immune function.

3. Initiate vaccine trials in the adjuvant setting.

4. Identify methods for immune monitoring to evaluate immunoresponsiveness prior to and following immune intervention.

5. Provide funding for the attraction of new and current investigators to collectively participate in immunotherapy trials.

D. Gene Therapy

1. Develop systemic delivery systems for non-toxic gene therapy through vector development, tumor-specific targeting and promotion, target-specific regulation and gene-specific regulation.

2. Develop animal models for translational research involving gene therapy.

3. Establish a mechanism for the appropriate peer review of translational research integrated within molecular-approached clinical trials.